

INDICATOR DILUTION CURVES IN ATRIAL SEPTAL DEFECT*

BY

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The indicator dilution technique has evolved into an invaluable method for the detection and localization of congenital and acquired cardiac shunts. The groundwork for much of the work in this field has been laid by Wood, Swan, and Helmholtz (1957); Swan (1959); Hetzel, Swan, and Wood (1959); Braunwald, Tanenbaum, and Morrow (1958) and Braunwald and Morrow (1960). Indocyanine green is the most commonly used indicator (Fox and Wood, 1957, 1960). The purpose of this report is to describe the use of indocyanine green in the diagnosis of the various types of atrial septal defects and associated congenital lesions. Dye dilution curves were recorded continuously from systemic arteries and the right heart by withdrawal of blood through a Gilford cuvette densitometer (Gilford *et al.*, 1953) by means of a Harvard constant rate withdrawal-infusion apparatus. The indicator dilution curves were recorded at a paper speed of 5 mm./sec., with 1-second time lines, using a photographic cathode-ray recording instrument.

Forty-three patients with atrial septal defect, either simple or complicated by other lesions, were studied. Standard techniques of right heart catheterization and systemic arterial cannulation with a thin-walled 18 G Cournand needle were employed. Two Lehman catheters (6 or 7F) were used for right heart catheterization. Systemic arterial and right heart dye dilution curves were usually recorded simultaneously (Swan *et al.*, 1958; Wood, Swan, and Marshall, 1958).

PRINCIPLES

The basic concepts of dye dilution curves in the normal subject and the patient with right-to-left or left-to-right shunts have been discussed and illustrated in detail (Samet *et al.*, 1962). The injection site is the anatomical site at which indocyanine green is introduced into the circulatory system. The sampling site is the area from which an indicator dilution curve is inscribed. The characteristics of the normal curve and the curves in the presence of a left-to-right or right-to-left shunt after right heart injection and systemic arterial sampling are well known. Localization of the site of the shunt is possible in the latter, but not former type of shunt when right heart injection and systemic arterial sampling are performed.

Left-to-right shunt site localization may be performed in a variety of fashions. These varied techniques consist either of constant injection site and variable sampling site techniques, or constant sampling site and variable injection site techniques. Braunwald *et al.* (1959) first used a peripheral systemic vein as the constant injection site, with the right heart chambers serving as the variable sampling sites. A break on the downstroke of the right heart curves is present at and distal to the site of the left-to-right shunt, and variation of the sampling site serves to localize the shunt site. Wood

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et al. (1958) have described an even more valuable and accurate technique. Two right heart cardiac catheters are employed, the constant dye injection site in the right heart being downstream to the varied right heart sampling sites. Appearance of the indicator material within a few seconds after downstream injection is diagnostic of a left-to-right shunt if right heart valvular insufficiency can be ruled out. Absence of this early appearance time in an adjacent upstream chamber localizes the left-to-right shunt to the right heart chamber in which an early appearance time is first observed as the sampling catheter tip is moved progressively downstream, i.e. superior vena cava, right atrium and ventricle, and finally pulmonary artery.

Variation of the left heart or aortic injection site provides an alternative method of left-to-right shunt localization. Braunwald *et al.* (1958) first described this technique. The left heart or aortic injection site at which a break on the downstroke of the systemic arterial indicator dilution curve first fails to appear localizes the shunt site. A variation of the right heart sampling technique outlined above may also be used. The left heart or aortic injection site at which a pulmonary artery dye curve early appearance time first fails to appear indicates the shunt site. These principles have been illustrated in detail (Samet *et al.*, 1962).

In general it has been our experience that left-to-right shunts can be detected and localized most decisively by the early appearance time approach. The interruption of the downstroke technique may on occasion result in less certain localization of such shunts.

RESULTS

The first patient (L. L.) is a 13-year-old white girl with an interatrial septal defect of the ostium secundum variety (without anomalous pulmonary venous connexion) proven at operation. Differential left-to-right shunting from the two lungs has been described repeatedly in this type of atrial

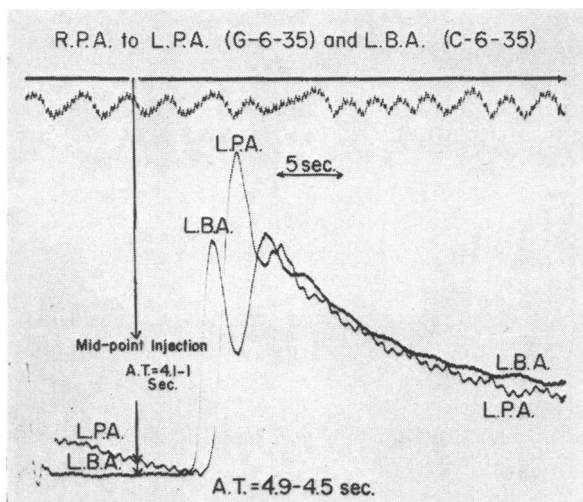


FIG. 1(A).—Indicator dilution curves after injection into the right pulmonary artery with sampling from the left pulmonary and brachial arteries. The respective dead space correction times for the left pulmonary artery and brachial artery sampling systems are 4.5 and 1 sec. respectively. The initial peak on the brachial artery curve represents the dye traversing the normal circulatory pathway: the second peak on the brachial artery curve and the initial peak on the pulmonary artery curve are a function of the magnitude of the left-to-right shunt. Fig. 1(B), 1(C), and 1(D) are from the same patient.

defect (Swan *et al.*, 1956a; Swan, Hetzel, and Wood, 1956b; Silver, Kirklin, and Wood, 1956), and is illustrated in Fig. 1A and 1B. In the former, indicator dye was injected into the right pulmonary artery and sampled from the left pulmonary and brachial arteries. In the latter, the dye was injected into the left pulmonary artery and sampled from the right pulmonary and left brachial arteries. The brachial artery curve after right pulmonary artery injection demonstrates an initial deflection (representing blood passing directly to the periphery) equal in size to the secondary deflection, representing blood that shunted from the left to the right atrium. After left pulmonary artery injection, the second peak (or downstroke interruption) on the brachial artery curve is much

less prominent than the initial peak. Furthermore, the left pulmonary artery curve after right pulmonary artery injection is much larger than is the right pulmonary artery curve after left pulmonary artery injection, despite the equal sensitivities at which the pulmonary artery curves were recorded. These data clearly demonstrate that the right pulmonary artery and lung contribute more to the atrial left-to-right shunt than do the left pulmonary artery and left lung. The pulmonary artery-brachial artery appearance time is about three seconds. The one second subtracted from the brachial artery appearance time is due to the dead space of the arterial sampling system. The pulmonary artery to pulmonary artery appearance times in Fig. 1A and 1B are corrected for the dead spaces of the right heart catheters (4.5 and 3 seconds respectively) at given sampling rates and are quite short: the

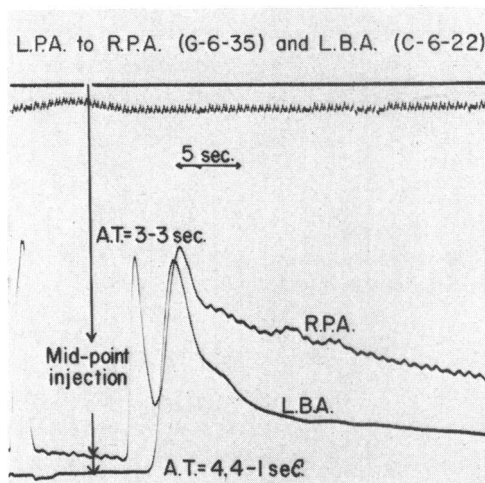


FIG. 1(B).—Left pulmonary artery injection; right pulmonary and left brachial arterial sampling. See text for details.

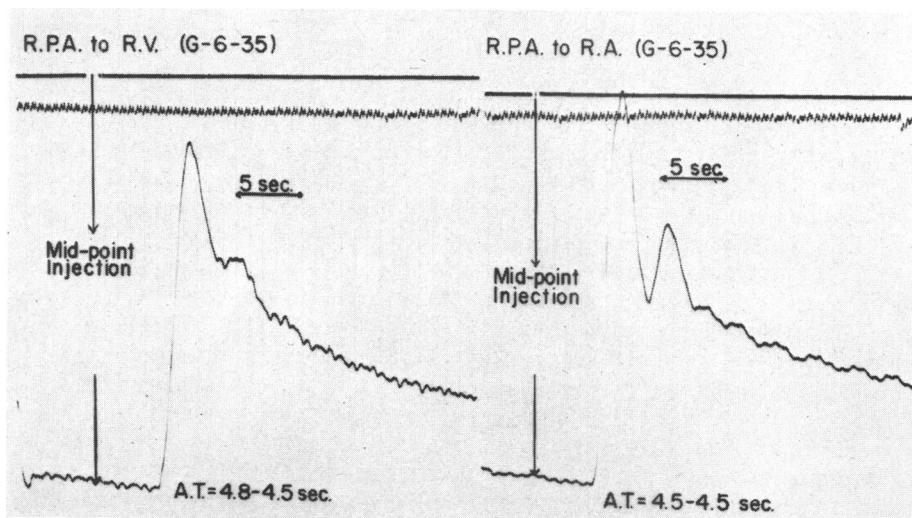


FIG. 1(C).—Right heart and systemic arterial sampling after pulmonary artery injection.

abbreviated appearance times are pathognomonic of a left-to-right shunt. Pulmonary artery injection with right heart sampling reveals that early appearance time is also noted in the right ventricle and right atrium (Fig. 1C) but not in the superior vena cava (Fig. 1D) or inferior vena cava thus placing the site of the left-to-right shunt in the right atrium. At operation a 3×4 cm. ostium secundum defect was closed by insertion of an elliptical plastic prosthetic patch.

Differential right (as compared to left) pulmonary artery left-to-right shunt is not invariably seen in the ostium secundum defect although it is the most common pattern. In R. W. (curves not shown) dye injection into the pulmonary arteries revealed approximately equal left-to-right shunting from the two pulmonary arteries. In J. McN., Fig. 2, the reverse of the common pattern was observed in that the degree of left-to-right shunting was greater after left pulmonary artery than after right pulmonary artery dye injection. The secondary peak deflection (indicative of the magnitude of the left-to-right shunt) is relatively more prominent after left than after right pulmonary artery injection. The anatomical observations in these two latter patients (in whom ostium secundum defects were found at operation) offered satisfactory explanations for the results of these indicator dilution studies.

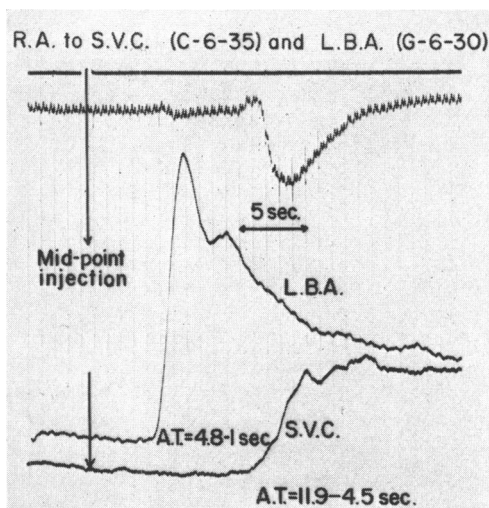


FIG. 1(D).—Superior vena cava sampling after right atrial injection. The length of the appearance time (compared to the right atrium) localizes the left-to-right shunt to the atrial level. The break on the downstroke of the brachial artery curve is readily seen.

The two pulmonary arteries usually make equal contributions to the left-to-right shunt in another variety of atrial septal defect, the ostium primum defect. In this anomaly left ventricular indicator injection results in abnormal systemic arterial and right heart dilution curves, whereas in the ostium secundum defect left ventricular injection fails to produce such results. In Fig. 3 (J. M., ostium secundum defect) left atrial injection results in early dye appearance in the right heart (right pulmonary artery) and an abnormal femoral artery curve with an obvious break on the downstroke. Left ventricular injection produces a normal systemic arterial curve and a delayed normal pulmonary artery appearance time. On the contrary in Fig. 4 (F. C., ostium primum defect) pulmonary vein injection also causes abnormal femoral and pulmonary artery dye curves. However, left ventricular injection is followed by an early pulmonary artery appearance time and a somewhat deformed femoral artery downstroke. Mitral regurgitation and an interventricular septal defect are the two defects that produce such data. In the patient under discussion (F. C.) at surgical repair a low atrial defect and a cleft mitral valve leaflet (producing mitral regurgitation) were observed. An interventricular septal defect was not found. It should be emphasized, however, that left atrial and left ventricular injection data may on occasion be difficult to analyze. For example in J. M., Fig. 5

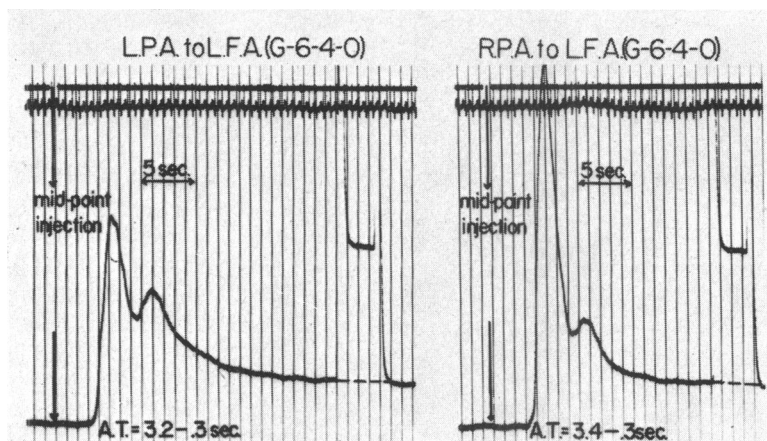


FIG. 2.—Disproportionate left-to-right shunting from the left pulmonary artery in ostium secundum defect.

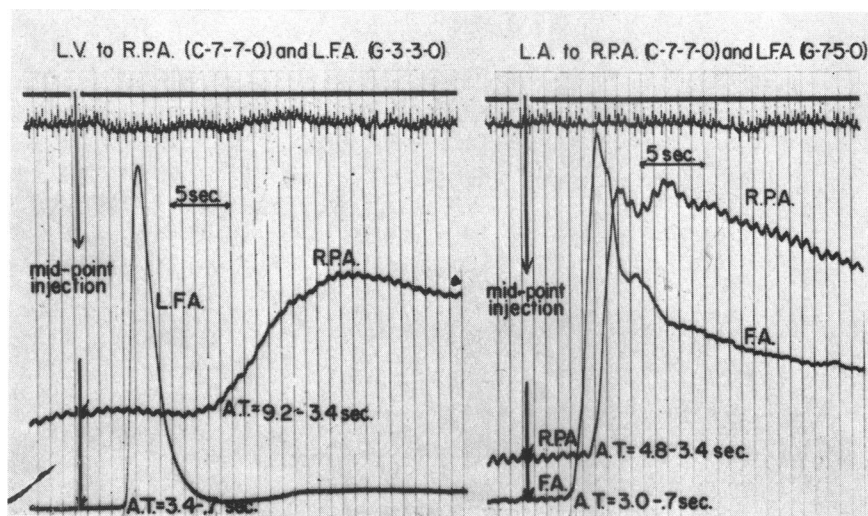


FIG. 3.—Pulmonary and systemic arterial dye dilution curves after left heart injection. A left-to-right shunt is noted from the left atrium but not left ventricle in ostium secundum defect.

(the same patient as in Fig. 3) left atrial injection near the mitral valve but in the left atrium resulted in normal arterial curves. Mid-left atrial injection gave obvious evidence of the left-to-right shunt at the atrial level. Errors in the opposite direction may also follow left atrial and left ventricular dye injection. Left atrial and left ventricular injection may both produce early pulmonary artery appearance times and deformed brachial artery curves in patients with typical ostium secundum defect. A forcible left ventricular dye injection near the mitral valve has been found responsible for such abnormal dye curves after left ventricular injection in patients with typical ostium secundum defects. These problems may usually be avoided by making multiple left atrial and left ventricular injections.

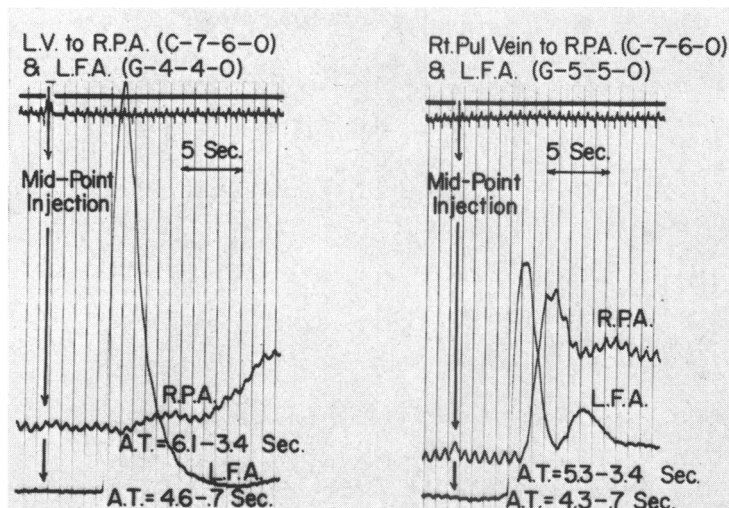


FIG. 4.—Pulmonary and systemic arterial dye dilution curves after left heart injection. A left-to-right shunt is noted from both the pulmonary vein and left ventricle in ostium primum defect.

Right-to-left shunts from the inferior vena cava and on occasion from the superior vena cava may be observed in patients with atrial septal defect. In ostium secundum defects the right-to-left shunt is usually greater after dye injection into the inferior than into the superior vena cava: the shunt may not be present from the latter vessel (Fig. 6). The femoral artery appearance time is shorter after inferior caval than after superior caval injection. The double-peaked systemic arterial curve is noted only after inferior vena cava injection. The diagnosis in this patient was proven at operation.

If the right-to-left shunt is larger from the superior than from the inferior vena cava (Fig. 7A and B)

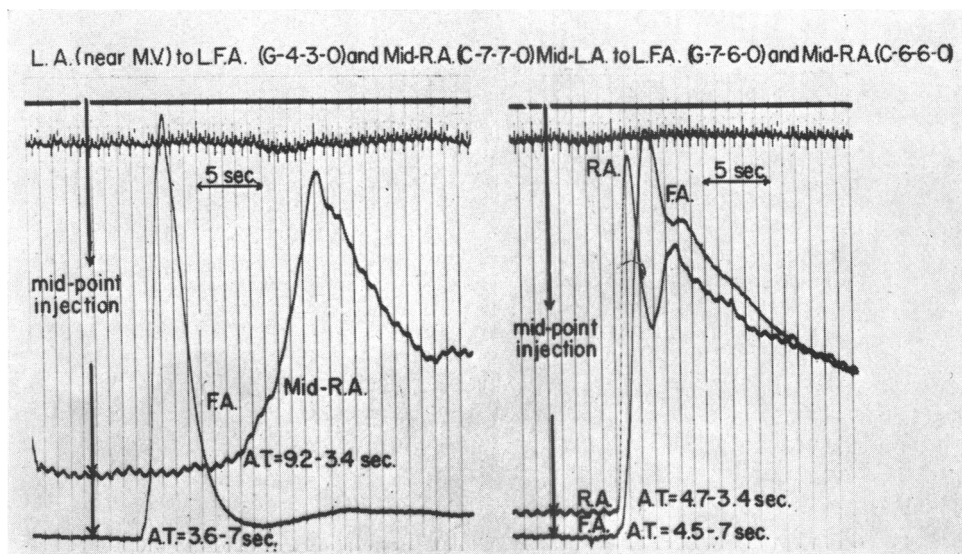


FIG. 5.—Two left atrial injection sites in ostium secundum defect. The importance of injection away from the mitral valve is evident. See text for detail.

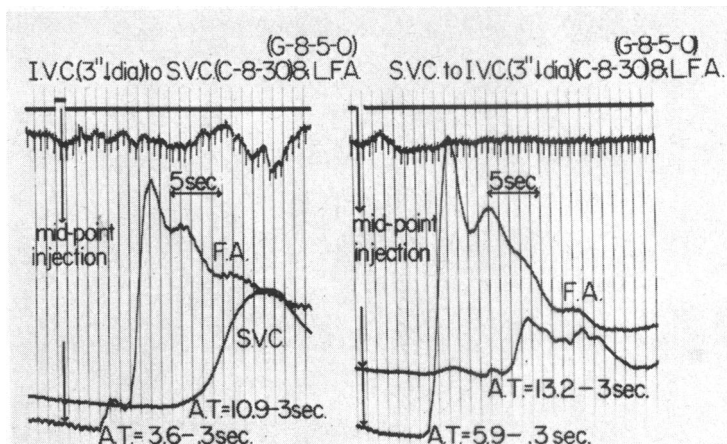


FIG. 6.—Right heart and systemic arterial dye dilution curves. A right-to-left shunt (with a double peak on the femoral artery curve) is present from the inferior but not the superior vena cava in an ostium secundum defect.

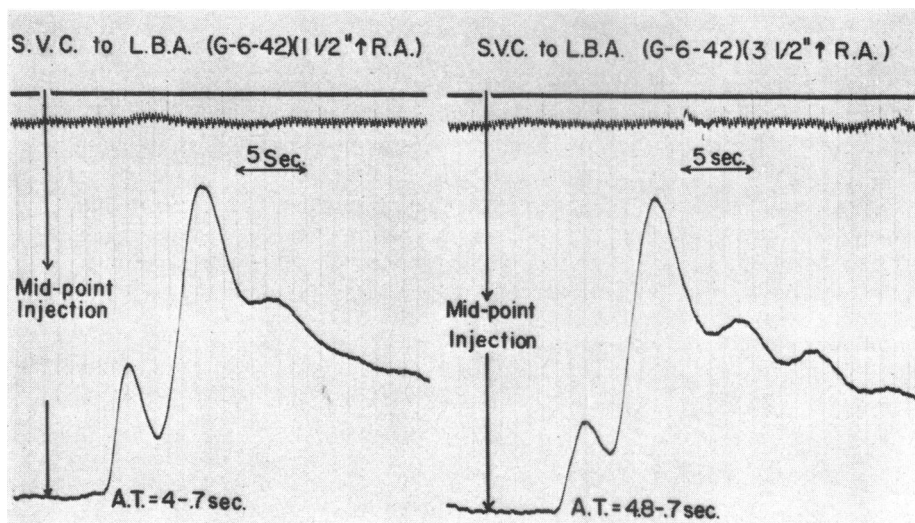


FIG. 7(A).—Prominent right-to-left shunt after superior vena cava injection in atrial septal defect.

a sinus venosus atrial defect with anomalous pulmonary venous drainage from the right upper and middle lobe should be strongly suspected. Marked differential right and left pulmonary artery left-to-right shunting is obviously a part of this disease complex. The diagnosis of sinus venosus defect with anomalous pulmonary venous connexion is more firmly established by analysis of the dye appearance times in the systemic artery after right and left atrial and pulmonary vein injection (Braunwald, Lombardo, and Morrow, 1960). In atrial septal defect with normal pulmonary venous drainage and only a left-to-right shunt, Braunwald noted that the appearance time of dye in arterial blood following pulmonary vein injection was on the average 0.2 sec. longer than that following left atrial injection. Right atrial injection appearance times averaged 3.8 sec. more than pulmonary

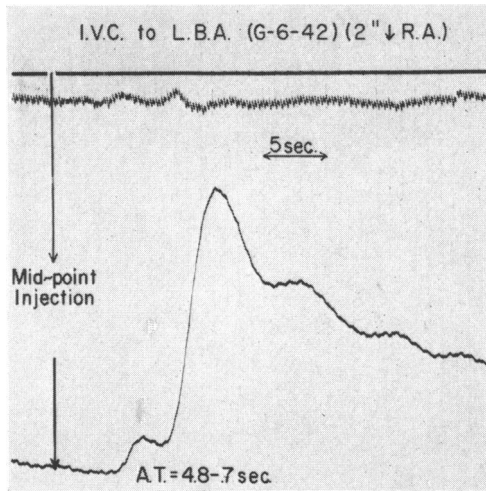


FIG. 7(B).—Inferior vena cava injection in the same patient as in Fig. 7(A). The right-to-left shunt is less evident.

vein appearance time. On the contrary in the sinus venosus variety of atrial septal defect with anomalous drainage of the right pulmonary veins, dye injected into the left atrium appeared in the peripheral artery 3.6 sec. (average time) earlier than following dye injection into the anomalous pulmonary vein. Right atrial and anomalous pulmonary vein appearance times differed by only 0.3 sec., average value. Furthermore the contours of the systemic arterial dye curves after right atrial and anomalous pulmonary vein injection were similar and differed from left atrial injection curves, whereas in the patient without anomalous pulmonary veins, the pulmonary vein injection curve contour resembled that of the left rather than the right atrium. Braunwald *et al.* (1960) did not observe abnormal systemic arterial dilution curves after left atrial injection in patients with the sinus venosus type of atrial septal defect. The dye dilution curves shown in Fig. 8 illustrate these concepts in a patient with a surgically verified sinus venosus defect with anomalous right upper and middle lobe pulmonary veins. The right pulmonary vein (to femoral artery) appearance time

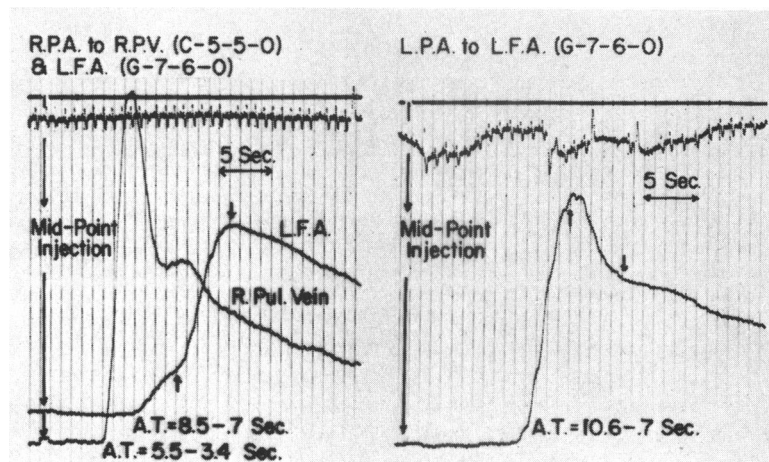


FIG. 8(A).—Right pulmonary vein and right atrial dye injection curves in a patient with surgically verified sinus venosus defect with anomalous pulmonary venous drainage.

is 9.7 compared to 10.3 after right atrial injection (Fig. 8A). Left atrial injection appearance time on the other hand was only 6.5 sec. (Fig. 8B). Differential left-to-right shunting from the two pulmonary arteries is clearly demonstrated in this same patient (Fig. 8C). Right pulmonary artery injection results in a small initial peak deflection (arrow pointing up) but a large secondary peak deflection representing the left-to-right shunt (arrow pointing down). The amplitude of these deflections is reversed following left pulmonary artery dye injection. It is worth noting that a left-to-right shunt from the left atrium is present in this patient (Fig. 8B): right pulmonary artery appearance time after left atrial injection is only 3.3 sec.

Difficulty may be encountered on occasion in making a decisive diagnosis of anomalous pulmonary vein associated with a sinus venosus defect (Fig. 9). Right pulmonary vein and right atrial injection (Fig. 9A) revealed identical femoral artery appearance times (3 sec.) and similar contours with smaller initial and larger secondary dye deflections. In addition the right pulmonary artery injection curve (Fig. 9B) was similar in appearance time and contour as after injection in these two sites. Left pulmonary vein injection (Fig. 9B) and left atrial injection (not shown) revealed femoral artery dye appearance time of 3.1 sec.; the contour of the arterial curve differed considerably from that after right atrial injection. Differential left-to-right shunting from the right pulmonary artery as compared with the left pulmonary artery is shown in Fig. 9C. At operation an ostium secundum defect was found, and the posterior inferior portion of the atrial septum was absent (the opening was $4\frac{1}{2}$ cm. in diameter). A finger could be passed from the right atrium through the defect to approximate the openings of the right pulmonary veins which were just to the left of the atrial septum. At present, we think that if the systemic arterial dye appearance time is similar from a pulmonary vein and from the right atrium (and if these are at least 3-4 sec. longer than left atrial injection appearance time), then an anomalous pulmonary vein is present. This aspect of indicator dilution curves will be discussed further.

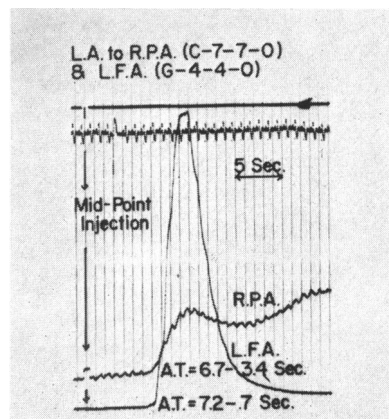


FIG. 8(B).—Left atrial injection site in the same patient as Fig. 8(A). See text for details.

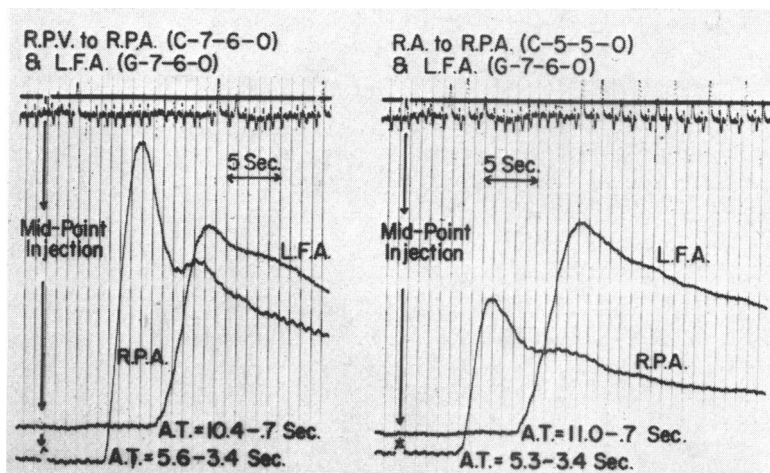


FIG. 8(C).—Disproportionate right pulmonary artery left-to-right shunting in the same patient as in Fig. 8(A) and 8(B). See text for details.

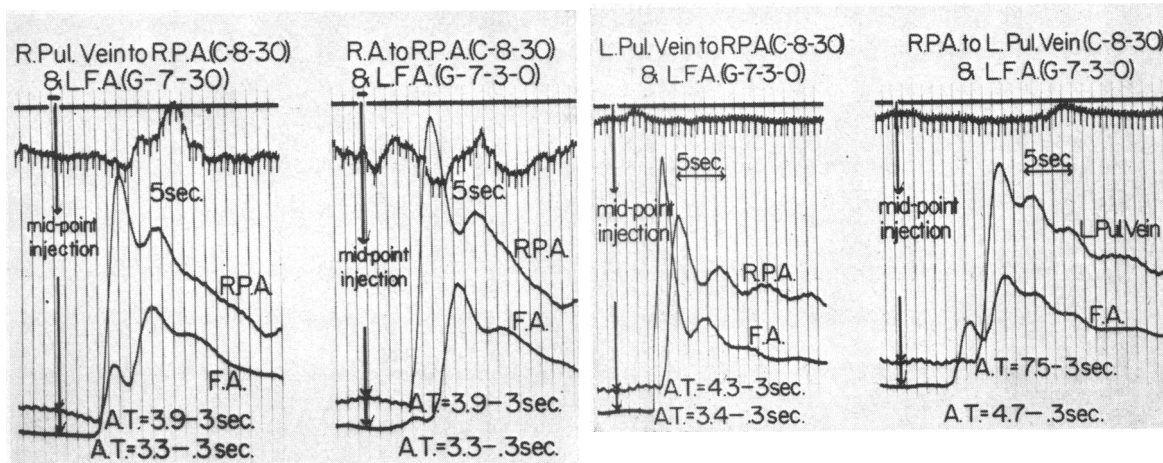


FIG. 9(A).—Right pulmonary vein and right atrial injection with pulmonary and systemic arterial sampling in ostium secundum defect; same patient as Fig. 6. See text for details.

FIG. 9(B).—Left pulmonary vein and right pulmonary artery injection in the same patient as Fig. 9(A).

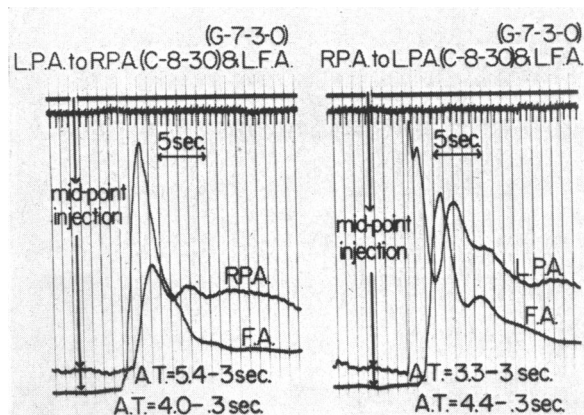


FIG. 9(C).—Differential pulmonary artery left-to-right shunting in the same patient as Fig. 9(A) and 9(B).

DISCUSSION AND SUMMARY

The clinical utility of indicator dilution curves in the detection and localization of congenital left-to-right and right-to-left shunts at the atrial level has been well documented. As with any diagnostic modality, experience has clarified both the special value and the limitations of this approach. Several points should be emphasized.

The right lung usually contributes proportionately more to the left-to-right shunt through the ostium secundum defect than does the left lung. The anatomical substrate for this observation lies in the fact that the right pulmonary veins usually empty into the left atrium near the defect while the left pulmonary veins empty at some distance from the defect (Swan *et al.*, 1956a, b). Differential right pulmonary artery shunting is even more pronounced in the sinus venosus variety of atrial septal defect, but is absent in ostium primum defects. On occasion, however, divergent findings may be noted in the ostium secundum defect (Fig. 2). In R. W. equal left-to-right shunting was seen after injection into the right and left pulmonary arteries. At operation an unusually prominent lip of the atrial septal defect was noted: it is postulated that this lip deflected right pulmonary vein flow so as to promote more equal mixing with left pulmonary vein flow before left-to-right shunting across the atrial defect. In J. McN., the left-to-right shunt was more prominent

after left than after right pulmonary artery dye injection—the reverse of the usual findings in the ostium secundum defect. At operation these physiological data were readily explained. The right atrium and right ventricle were rotated to the left and lay almost entirely to the left of the midline. Upon opening the right atrium it was seen that the left pulmonary veins opened immediately opposite the atrial defect: the openings of right pulmonary veins could not be seen but could be palpated only by passing a finger at an acute angle around the posterior rim of the defect.

Since differential right pulmonary artery left-to-right shunting is not pathognomonic of the sinus venosus defect, other criteria must be sought to permit diagnosis of this defect by indicator dilution curves. A greater right-to-left shunt after superior than after inferior vena cava injection raises the strong possibility of a sinus venosus defect. Comparison of systemic arterial appearance times after right atrial, left atrial, and pulmonary vein injection also aid in the diagnosis of anomalous pulmonary venous drainage. If the pulmonary vein injection curve is similar in contour and appearance time to left atrial injection, left atrial insertion of the pulmonary vein may be inferred. If the pulmonary vein to systemic arterial curve is similar to right atrial injection (and both are longer than left atrial injection appearance time), anomalous pulmonary venous drainage may be deduced. These conclusions may be complicated however by the fact that a double-peaked systemic arterial dilution curve may have two meanings—the first peak may represent a right-to-left shunt and the second the normal circulatory pathway; or alternatively the initial peak may represent the normal circulatory pathway and the second peak the left-to-right shunt. These potential problems may be solved by multiple right and left indicator injections and analyses of both appearance time and peak concentration time as well as the interval from indicator injection to appearance of a break on the downstroke of the systemic arterial curve.

Non-uniform indicator distribution after intravascular injection may lead to diagnostic errors. Left atrial injection near the mitral valve may fail to reveal a left-to-right shunt in an ostium secundum defect. Left ventricular injection near the mitral valve in turn may lead to an incorrect diagnosis of mitral regurgitation or a ventricular septal defect. Despite these minor problems indicator dilution curves have become a major method of investigation in the study of patients with various types of atrial septal defect.

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